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Study of Beta Cell Function in Patients of Diabetes and It's Association with Prevalence of NAFLD

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Abstract

Background: *Non Alcoholic Fatty Liver Disease (NAFLD) is becoming modern hepatic pandemic and NAFLD co-existing in patients with diabetics is supposed to have reduced beta cell function. Patients with NAFLD who have type 2 diabetes are particularly at risk of developing NASH and they are at higher risk of developing cirrhosis, also have poor glycemic control owing to reduced beta cell function. So identifying the patients with diabetes having NAFLD and β cell functional status could estimates the future risk and help in slowing the progression and prevention of chronic liver disease and various complications of Diabetes.*

Material: *This was a cross sectional observational study conducted in department of medicine, N.S.C.B., MCH, Jabalpur in which 100 cases of diabetes were taken who satisfied inclusion and exclusion criteria. Abdominal USG was used for evidence of fatty liver and it's grading and fasting serum levels of insulin (FIL) and fasting blood sugar (FBS) were used to calculate HOMA-β value to get beta cell function.*

Observation: *HOMA-β values were calculated for all the patients of DM, which showed that lower mean HOMA-β values in patients with NAFLD and Diabetes i.e.37.56±24.03 as compared to 60.96±96.62 in Non NAFLD group of patients. β cell function was deranged in the patients with high BMI, Waist circumference. NAFLD group of patients have higher prevalence of diabetes related complications as compare to Non NAFLD group. Prevalence of NAFLD was slightly more in females-56.6%(n=30) as compared to males-55.32%(n=26).We found higher Mean BMI, Waist circumference, Triglycerides, FBS,FIL in cases with NAFLD (24.83±2.42, 95.11±12.46, 180.07±51.35, 176.13±66.79, 13.59±15.42) as compare to non NAFLD (22.41±2.16, 85.84±9.86, 139.09±39.27, 134.8±34.41, 6.79±4.49) respectively. Lower HOMA-β values were significantly associated with raised BMI and WC.*

Conclusion: *As NAFLD is highly prevalent in diabetics, possibility of NAFLD should be considered in all of them. Patients with Diabetes who also have NAFLD, observed to have relatively reduced β cell function, However it is not significantly associated with Non NAFLD group probably because of already reduced β cell function reserve in diabetics However progressive decline in β cell function could estimate future risk of NASH and complications of diabetes. It seems reasonable to expect that early diagnosis of NAFLD and early intervention with strict glycemic control and weight loss would prevent complications.*

Introduction

Nearly unlimited supplies of energy-dense foods and technologies that encourage sedentary behaviour have introduced a new threat to the survival of our species: obesity and its co-morbidities. Foremost among the co-morbidities is type 2 diabetes. Type 2 diabetes mellitus (T2DM) has emerged as a pandemic and India, with >60 million people with diabetes, has the second largest diabetic population of the world.[1]

There is an evidence of multiple factors interplaying role in pathogenesis of NAFLD in diabetes and reduced β cell function is one of them. NAFLD predicts the development of type 2 diabetes and vice versa, and each condition may serve as a progression factor for the other. Although the association of diabetes and NAFLD is likely to be partly the result of a "common soil, through interrelated metabolic pathways currently only partly understood, diabetes appears to accelerate the progression of NAFLD to nonalcoholic steatohepatitis, defined by the presence of necro inflammation, with varying degrees of liver fibrosis.

Although obesity often leads to insulin resistance, only a subset of obese, insulin-resistant individuals progress to type 2 diabetes. In both animal models and humans, the triggering factor is β-cell failure, which involves a decrease in β-cell mass and deterioration of key β-cell functions such as glucose-stimulated insulin secretion (GSIS).

Epidemiological studies suggest the prevalence of NAFLD to be around 9-32% in general Indian population, with a higher incidence amongst overweight/obese and diabetic/ prediabetic patients.[2-8]

Prevalence of NAFLD in type 2 diabetes patients (India) varies from 12.5% to 87.5%.[4-6,8]Apart from cardiovascular disease, liver failure is another major cause of excess morbidity and mortality in type 2 diabetes with NAFLD. Therefore, it is important for physicians to be aware of the high likelihood that their patients with type 2 diabetes have NAFLD. Another important fact is, diabetes is associated with metabolic syndrome and both of these have greater incidence of NAFLD, more over persons with NAFLD have reduced β cell function and patients of NAFLD with diabetes, due to reduced β cell function supposed to have hyperglycemia relatively refractory to OHA leading to increased requirement of dose of OHA's and thus predisposes to greater risk of side effects.

Material and Methods

This study was an observational cross sectional study conducted at the department of General Medicine, NSCB Medical College & Hospital, Jabalpur from March 2016 to Aug. 2017on 100 patients with diabetes who were willing for study, satisfied the inclusion and exclusion criteria.

Inclusion Criteria for cases

- Adults (>21yrs) with type 2 diabetes who are previously diagnosed to have DM type2 and currently on dietary glycemic control or on oral hypoglycemic agents (OHA's) or newly diagnosed DM type 2 according to International Diabetes Federation Criteria[9]

Exclusion Criteria for cases

- All type 1 Diabetics.
- Patients with Multi Organ Dysfunction Syndrome.
- Patients on Injectable Insulin Preparation.
- Known cases of alcoholic liver disease or history of significant alcohol consumption[10]
- Known or newly diagnosed cases of infective hepatitis and parasitic infections damaging liver cells.
- Cases with history of consumption of hepatotoxic drugs or chemicals.
- Cases with family history of liver dysfunction or liver cancers

In each patient selected, history, anthropometric measurements and clinical findings were recorded and relevant investigations were done. Abdominal Ultrasonography was done to detect fatty liver and simultaneous grading of fatty liver was done at the

same time by same radiologist in each study subject. HOMA-β was calculated by estimating Fasting insulin levels (FIL) and Fasting blood sugar levels by simultaneously withdrawn blood sample after overnight fasting of at least 8 hours. β cell function was calculated using HOMA – β[11](Homeostatic Model Assessment β).

$$\text{HOMA-}\beta\ \% = \frac{360 \times (\text{Fasting plasma insulin}\}\text{mIU/L}}{Glucose(\frac{mg}{dl}) - 63}$$

The normal plasma fasting insulin levels taken as < 25 mIU/ L.[12,13]

Other associated blood tests were performed and finally study subjects were divided in to 2 groups (NAFLD group and Non NAFLD group) and comparisons made between the 2 groups on various parameters. For skewed deviation of data for HOMA – β, non parametric tests were applied.

Modified NCEP: ATP III and IDF criteria for the diagnosis of metabolic syndrome is used for defining abnormal lipid profile (TG, Total Cholesterol), waist circumference, blood pressure, fasting plasma glucose and obesity.[14]

Results

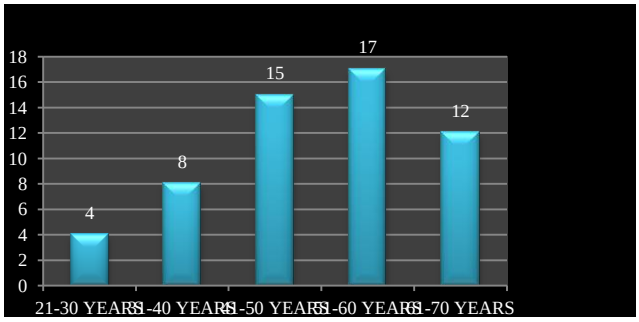
We studied total 100 cases of type 2 diabetes in the study period in which 47 cases were males and 53 were females.

We included subjects of age groups ranging from >21 years to 70 years with mean age of 49.75 ± 11.681 .Mean age of cases with NAFLD was 50.66±11.68 and mean age of cases without NAFLD was 48.59±11.45.(χ^2=1.9;p>0.05). Majority of the cases belong to age group 41-60 years (n=60) Highest prevalence of NAFLD was found in age group 61-70 Years (70.6%). Prevalence of NAFLD was 56% in our study with slight female preponderance (56.6%).

Age Wise Distribution of NAFLD Cases (χ^2=1.9;p>0.05)

AGE GROUP	CASES	TOTAL CASES
21-30 YEARS	04 (50%)	8
31-40 YEARS	08 (53.3%)	15
41-50 YEARS	15 (55.5%)	27
51-60 YEARS	17 (51.5%)	33
61-70 YEARS	12 (70.6%)	17
Mean±SD	50.66±11.68	49.75 ±11.68
TOTAL	**56**	**100**

Age Wise Distribution of NAFLD Cases



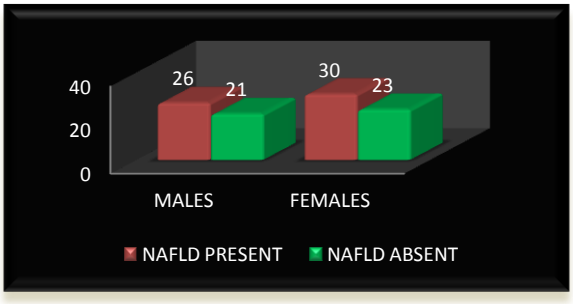
The following table shows the gender wise distribution of NAFLD cases. The prevalence of NAFLD among males was 55.30% and among females was 56.60%**.** The chi square value was 0.02 with p value>0.05 and there was no significant difference in NAFLD between the genders in both the groups.

Gender Wise Distribution of NAFLD

Gender	NAFLD Present (n=56)	NAFLD Absent (n=44)	Total
Male	26 (55.30%)	21 (44.70%)	47 (100%)
Female	30 (56.60%)	23 (43.40%)	53 (100%)
Total	56	44	100

χ^2=0.02;p>0.05

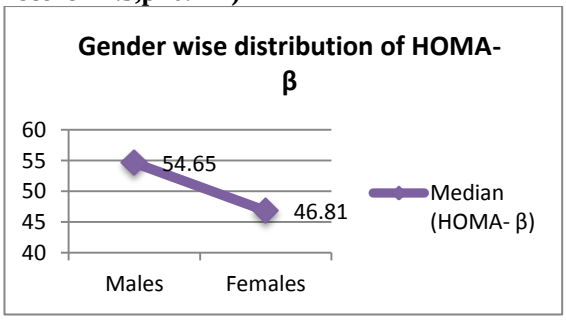
Gender Wise Distribution of NAFLD



Gender wise distribution of HOMA- β

Gender	Total cases	Median (HOMA-β)
Males	**47**	**54.65**
Females	**53**	**46.81**

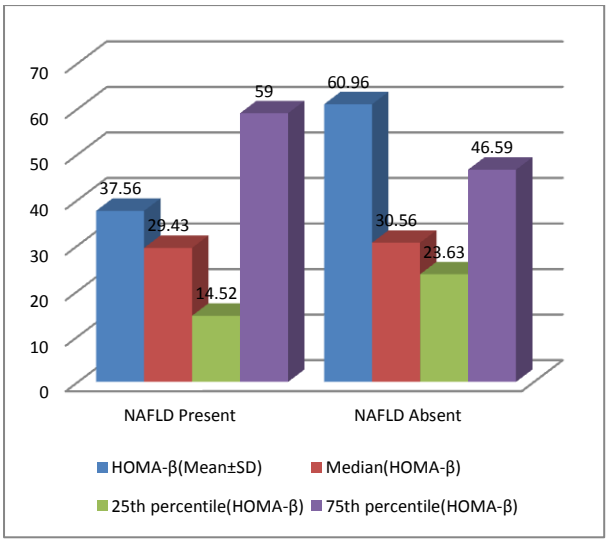
(z score=-1.3,p=0.177)



Comparison of β Cell Function between NAFLD and Non NAFLD Group

HOMA-β	Cases with NAFLD (n=56)	Cases without NAFLD(n=44)
Mean±SD	37.56±24.03	60.96±96.62
Median	29.43	30.56
25th percentile	14.52	23.63
75th percentile	59	46.59

t=1.57;p=0.12, after log transformation t=0.05,p=0.96 and on applying non parametric Mann Whitney Wilcoxon test Z=0.007,p=0.99



The mean BMI,WC,TG,FBS and Fasting insulin level were higher in NAFLD group than Non NAFLD group (t= 4.08,4.04,4.38,3.73,2.83) respectively with p value <0.001 that was highly significant. The mean HOMA-β value were lower in NAFLD group than Non NAFLD group but it was not statistically significant (t test- t=1.57, p=0.12, after log transformation t=0.05,p=0.96 and on applying non parametric Mann Whitney Wilcoxon test Z=0.007,p=0.99).

Comparison of Mean BMI, Waist Circumference, TG, FBS, Fasting Insulin Level & Homa--β Between NAFLD and Non NAFLD Group

Variables	Cases with NAFLD (n=56)	Cases without NAFLD(n=44)	Significance
BMI(Kg/mtr2)	24.83±2.42	22.41±2.16	t=4.08 p<0.001
WC(Cm)	95.11±12.46	85.84±9.86	T=4.04 P<0.001
TG(mg/dl)	180.07±51.35	139.09±39.27	t=4.38 p,0.001
FBS(mg/dl)	176.13±66.79	134.8±34.41	t = 3.73 p<0.001
Fasting Insulin Levels (mIU/L)	13.59±15.42	6.79±4.49	t = 2.83 p<0.001
HOMA-β	37.56±24.0	60.96±96.6	t =1.57 p>0.05

The mean AST and ALT levels were higher in NAFLD group than Non NAFLD group with (t= 2.23,2.19) respectively with p value <0.05 that was statistically significant.

Comparison of Mean AST and ALT Levels between NAFLD and Non NAFLD Group

Variables	Cases with NAFLD (n=56)	Cases without NAFLD(n=44)	Significance
AST(IU/L)	51.35±35.21	37.64±23.02	t=2.23 p<0.05
ALT(IU/L)	53.6±30.35	41.67±22.14	t=2.19 P<0.05

Comparison of Complications of Diabetes between NAFLD and Non NAFLD Group

Complications	Cases with NAFLD (n=56)	Cases without NAFLD(n=44)	Total	SIGNIFICANCE
Diabetic Retinopathy	14 (77.7%)	4 (22.2%)	18	χ^2=3.2;p>0.05
Diabetic Nephropathy	18 (75%)	6 (25%)	24	χ^2=3.6;p>0.05
Diabetic Neuropathy	22 (68.75%)	10 (31.25%)	32	χ^2=2.39;p>0.05
Diabetic Gastroparesis	19 (52.77%)	17 (47.22%)	36	χ^2=0.07;p>0.05
Cardiovascular complications	27 (69.2%)	12 (30.8%)	39	χ^2=3.12;p>0.05
Cerebrovascular accidents	4 (66.6%)	2 (33.3%)	06	χ^2=0.014;p>0.05
Hypertension	32 (65.3%)	17 (34.7%)	49	χ^2=2.67;p>0.05

Above table shows that incidence of various complications of Diabetes Mellitus were relatively more in NAFLD group as compare to Non NAFLD group. However these correlations were not found statistically significant between the two groups.

Comparison of Beta Cell Function (Homa β) among BMI, WC, Insulin Resistance and Various Complications of Diabetes

Parameters	Status	No.of cases	Median (HOMA-β)	P -value
Diabetic Retinopathy	Present	18	48.79	0.20
	Absent	82	58.31	
Diabetic Nephropathy	Present	24	43.54	0.18
	Absent	76	52.70	
Diabetic Neuropathy	Present	32	48.26	0.26
	Absent	68	55.25	
Diabetic Gastroparesis	Present	36	53.74	0.40
	Absent	64	48.68	
Cardiovascular complications	Present	39	46.33	0.07
	Absent	61	57.03	
Insulin Resistance	Present	49	38.31	0.0001*
	Absent	51	63.81	
High BMI >23(Over weight to Obese)	Present	60	40.60	0.005*
	Absent	40	57.10	
Increased WC	Present	62	40.95	0.01*
	Absent	38	56.35	

***Statistically significant**

The Median HOMA- β values in various complications of diabetes were less as compare to cases without complications. However this is not found significant. While cases with High BMI and Increased WC were significantly associated with reduced β cell function.

Discussion

Diabetes Mellitus type-2 is basically a disease of insulin resistance. With the progression of the disease, amount of insulin secretion and β cell reserve of pancreas also starts declining and leads to uncontrolled type 2 DM and complications related to the disease.

Hence we studied the β cell function in the patients of type 2 DM and correlated it with clinical profile.

Most of the cases of type 2DM fall in age group 41-50 and 51-60 years with mean age of 49.75±11.681 years. Percentage of NAFLD was highest among age group 61-70 years i.e. 70.6% (12 out of 17 cases).One of the study done on Indian population previously also reported shifting trend of occurrence of NAFLD in later ages.[17,18]

Again out of 100 cases, 47 were males and 53 patients were females. Out of all female patients, 30/53 patients have NAFLD as compare to 26/47 male patients, showing NAFLD prevalence in female diabetics to be 56.6%.In some previous studies, NAFLD was considered to be more common among women.[22,23] In others it was reported to be more prevalent among men.[24,25]

In our study the overall prevalence of NAFLD in patients with Diabetes mellitus was 56% which is found consistent with previous studies.[16,17]

In our study we found relatively lower mean and median of HOMA-β in NAFLD as compare to Non NAFLD. However it was not statistically significant.

Li FP et al[26] Observed that no significant difference of HOMA-beta and late phase insulin secretion index between the NAFLD group and control group. However they observed that early phase insulin secretion index in the NAFLD group was lower than that in the control group significantly.

Fatty liver involvement in patients of diabetes again leads to liver dysfunction in the form of raised liver enzymes i.e. serum amino-transferases levels. In our study we found the mean AST and ALT levels were higher in NAFLD group as compared to Non NAFLD group (t=2.23,2.19) respectively with p value<0.05, that was statistically significant. Similar results observed in previous studies.[17]

A mild to moderate (1.5 to 4-fold) elevation of the serum AST or ALT level, or both, is common, The serum ALT level is usually greater than the AST level in NAFLD, in contrast to the pattern of alcoholic hepatitis.[21]

In T2DM patients, chronic mild elevations of liver enzymes are frequently encountered, Emphasizing the already known fact that T2DM has a strong association with NAFLD, including its severe form NASH.

ALT appears to have a role in gluconeogenesis and seems to be more related to liver fat accumulation than AST.

As we observed, majority of the cases were over-weight i.e 42%.Among over weight patients, prevalence of NAFLD was 64.30% (n=27) and this prevalence increases to 84.6% (n=16/18) among obese patients and 100%(n=5/5) morbidly obese cases have NAFLD. The mean BMI was

significantly higher in cases with NAFLD (24.83±3.42) as compared to Non NAFLD group i.e.22.41±2.16 (t test=4.08,p value=0.001) which is found statistically very highly significant. Studies supporting this observation also showed high likelihood of NAFLD in obese diabetics.[16,18,19,21]

The present study also reported positive correlation of waist circumference with occurrence of NAFLD and reduced beta cell function as mean waist circumference and median HOMA-β values were 95.11±12.46 and 40.95 respectively among cases with NAFLD and 85.84±9.86 and56.35 respectively in Non NAFLD group (t test- 4.04,z score -2.57p value<0.05) which is statistically highly significant. Studies based on waist circumference and occurrence of NAFLD showed positive association of increased waist circumference and presence of NAFLD. [18,21,28]

In our study high TG, high serum total cholesterol were significantly associated with increased prevalence of NAFLD asreflected by higher mean TG and mean total cholesterol in NAFLD group (180.07+51.39,198.48+41.96) compared to Non NAFLD group139.09+39.27,177.57+22.96 respectively), (t test=4.38,2.97 respectively, P value<0.05), similar correlation is reported in various studies.[18,19,27]

Among various macrovascular and Microvascular complications of Diabetes (CVS and CNS involvement, diabetic retinopathy, diabetic nephropathy, diabetic gastro paresis and diabetic neuropathy) we have not found any statistically significant positive correlation with NAFLD and beta cell dysfunction. However present study observed relatively lower median values of HOMA-β in patients with complications, except diabetic gastroparesis in which converse is seen but it was not found statistically significant. Nathalie C. Leiteet al[28] also didn't find positive correlation with presence of complications among NAFLD, However they found positive correlation with NAFLD and diabetic nephropathy.

Most common complication of Diabetes was found in the form of cardiovascular involvement (39% cases) in our study.

We found statistically significant association with lower median HOMA-β and obesity in terms of raised BMI and high WC.Similar observations made by Fumiaki Imamura and associates.[29]

Conclusion

Prevalence of NAFLD in cases with DM was 56% which is higher than general population, also Prevalence tends to increase with increasing age and Slight Female preponderance of NAFLD. Relatively reduced beta cell function was observed in cases with NAFLD in terms of lower median value of HOMA-β, However it was not statistically significant and needs to be proven in further studies. Levels of AST and ALT were significantly raised in cases with NAFLD than in cases without NAFLD. Mean FBS,TG, FIL, BMI, Waist Circumference also were Significantly raised in subjects with NAFLD. Significantly reduced Beta cell function is associated with raised BMI and waist circumference and hence correlated well with Obesity. Majority of cases with NAFLD have grade 1 fatty liver .Obese patients have more prevalence of NAFLD as compare to non-obese. Obesity has positive correlation with occurrence of NAFLD.

Median HOMA-β is relatively reduced in cases with various complications of DM as compare to cases without complications. Most common complication of Diabetes was found in the form of cardiovascular involvement (39% cases)

As reported from various studies the high prevalence of NAFLD in patients with diabetes, the possibility of NAFLD should be considered in all of them. These patients with NAFLD have high propensity of IR and reduced β cell function than patients without NAFLD, So are at higher risk of developing complications of diabetes, NASH and cirrhosis. Also obese diabetic patients have higher incidence of NAFLD and reduced β cell function as compared to non-obese patients. Due to reduced β cell function supposed to have

hyperglycemia relatively refractory to OHA leading to increased requirement of dose of OHA's which predisposes to greater risk of side effects of OHA's and also poor glycemic control and early onset micro as well as macrovascular complications of diabetes. It seems reasonable to predict that early diagnosis of NAFLD and early intervention with strict glycemic control and weight loss would prevent further complications.

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